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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,022	05/04/2001	Joseph D. Gold	091/005P	7806

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/849,022	GOLD ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,8,9,13 and 15-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,6,8,9,13 and 15-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *04 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed April 2, 2004 have been fully considered but are not persuasive. The amendment has been entered. Claims 1-3, 6, 8, 9, 13 and 15-36 are pending.

This application has been transferred to Deborah Crouch, Ph.D. AU 1632, whose contact information can be found at the end of this office action.

Applicant's request for an interview is noted. However, time did not permit the examiner to telephone applicant as request, especially in view of the outstanding rejections.

The obviousness-type double patenting rejection made in the previous office action over 10/039,956 is withdrawn because of applicant's arguments.

The rejections made under 35 U.S.C. 112, second paragraph in previous office action have been withdrawn because of applicant's amendments.

Applicant's arguments and amendments to the claims have overcome the rejection of claims 8-10 under 35 U.S.C. 102 (b) over Pederson (WO 97/47734); the rejection of claims 1-3, 5-6, 8-10 and 16-17 under 35 U.S.C. 102(b) over Bodnar (WO 99/20740); claims 10, 11, 14, 22 and 23 under 35 U.S.C. 103 over Bodnar in view of Feng; and claims 8 and 9 under 35 U.S.C. 103 over Thomson and Bradley presented in the office action mailed January 16, 2004.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 8 and 9 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 62 and 63 of copending Application No. 09/530,346 for reasons presented in the office action mailed January 16, 2004 for reasons presented in the office action mailed January 16, 2004.

Applicant has agreed to submit a terminal disclaimer once allowable subject matter is indicated in the present application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, 8, 9, 13 and 15-36 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) methods of obtaining or producing genetically altered pluripotent human ES cells comprising culturing pluripotent ES cells in the absence of feeder cells in a culture environment that contains an extracellular matrix and a fibroblast conditioned medium, and transfecting the human ES cells with a polynucleotide encoding a protein operably linked to an hES cell specific promoter to produce genetically altered pluripotent human ES cells that are undifferentiated and 2) methods for producing genetically altered differentiated cells comprising obtaining a culture comprising pluripotent human ES cells in the absence of feeder cells in a culture environment that contains an extracellular matrix and a fibroblast conditioned medium, transfecting the human ES cells with a polynucleotide to produce genetically altered

pluripotent human ES cells and causing the genetically altered cells to differentiated into neural cells and hepatocytes, does not reasonably provide enablement for the methods where the hES cells are grown in the absence of feeder cells in a culture environment that contains an extracellular matrix for reasons presented in the office action mailed January 16, 2004, and in view of applicant's amendments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is not found to be enabling with regard to culturing the human ES cells with an extracellular matrix, but without fibroblast conditioned media. While the specification teaches that hES cells can be grown in the absence of feeder cells in the presence of an extracellular matrix such as Matrigel™ or laminin, the specification only provides guidance for the media as conditioned fibroblast media. Lim et al 2002 states the specific factors required for the growth of hES cells, secreted by mouse embryonic fibroblast, is still not known. Thus clearly more than an extracellular matrix is required; that some particular factors are required to support the growth of human ES cells. The new limitation "encoding a protein operably linked to an hES cell specific promoter" has been added because if the promoter is active while the hES cells are undifferentiated and is also active in differentiated cells, there will be no enrichment for hES cells using this promoter.

New claims 24-26 are not enabled because the PGK promoter is active in differentiated cells types. Thus the limitation that genetically altered hES cells express the protein while undifferentiated not enabled as the protein would also be expressed in any differentiated cells produced by the cells. Hamaguchi teaches that the PGK promoter is active in mouse ES cells and differentiated cells (page 10783, col. 1, parag. 1).

Applicant argues that case law establishes that applicants are not required to limit their coverage to the working examples. Applicant argues that the office seeks to limit their

coverage to conditions that were exemplified in the working examples. Applicant argues that the working examples are to features that are not critical to the new feeder-free culture method described and claimed. Applicant cites *In re Peters,* 221 USPQ952 (fed. Cir. 1983) and *In re Rasmussen,* 211 USPQ 323 (CCPA 1981) for the argument that applicant need not put noncritical limitations in their claims. Applicant argues that the specification states (page 12, lines 34-37) pPS cells can be cultured in the presence of the usual components to enhance cell survival, including isotonic buffer, essential minerals and with serum or a serum replacement. Applicant argues that the description goes on to state that conditioned media is a possible nutrient medium. Applicant argues that other cells can be used in place of fibroblasts to produce conditioned media. These arguments are not persuasive.

The office is in no-way attempting to unfairly limit applicant's claims to the working examples without reason. As presented in the previous office action, those nutrients required for hES cell growth were unknown in the art at the time of filing (See Lim (2002)). The present specification provides no guidance on the media for the growth of hES cells, other than that in the working examples. The rejection contains a limitation to fibroblast growth factor conditioned media because that is the only guidance provided in the specification on the growth of hES cells in the absence of feeder cells. As Lim stated, feeder cells were required for hES cell growth, so there would need to be a substitution for the factors provided by feeder cells. Further, Lim also taught that such factors were not known. An extracellular matrix is composed on elements of the matrix in which cells grow/reside, but it would not produce any factors. Thus, the only means through which the artisan could implement the claimed invention is to use fibroblast-conditioned media. Thus, the examiner considers the use of conditioned media to be a critical element to the method and the resulting cells. Critical elements must be in claim for the claim to be fully enabled. Other

cells, which would substitute for fibroblast, also cannot be predictably determined, as the factors secreted by these other cells would vary.

Applicant states that the specification has been amended to incorporate phraseology present in priority document 60/213,739 that feeder free systems can be practiced by synthetically assembling the medium by the addition of growth factors directly to the medium. This argument is not persuasive.

The breakdown of all factors secreted by fibroblasts was not known at the time of filing. Lim teaches this fact. Thus, the addition of specific factors individually, directly to the medium is not enabled. The skilled artisan would not know which factors to add or in what concentrations. Further, that such addition is unpredictable, LIF, which is known to prevent differentiation of mouse ES cells, has no effect on inhibiting differentiation of hES cells. Thus, no teaching in the art for hES or mess cells could possibly provide guidance for the addition of factors randomly to media to promote the growth of undifferentiated hES cells as claimed.

Applicant states that scientists at Geron have achieved the growth of hES cells in non-conditioned medium with added growth factors. This argument is not persuasive.

Applicant should file a declaration under 35 U.S.C. 1.132 signed by someone with direct knowledge of the conditions. The declaration should contain details as to the supplements to the medium, and where such suggestion can be found in the present specification. Such a declaration can only support the disclosure in the present specification and cannot add any critical teachings for the implementation of the claims.

Applicant argues that the limitation of the hES cells to pluripotent ES cells is unreasonable as producing a human is unreasonable. This argument is not persuasive.

A claim has to be enabled for its entire breadth. Reasonable or unreasonable, that is the case law. Applicant had not enabled totipotent hES cells for reasons of record. Applicant is reminded that all totipotent cells by their nature are pluripotent.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 24 -26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24-26 are confusing as to whether the protein is only to be expressed in undifferentiated ES cells and not the differentiated cells produced from the genetically altered ES cells.

The claims are free of the prior art. At the time of the present invention the prior art did not teach or suggest the claimed methods for producing a population of genetically altered human ES cells comprising culturing human ES cells essentially feeder cell free on an extracellular matrix and transfecting the cells with a polynucleotide comprising a DNA sequence encoding a protein operably linked to a promoter that promotes transcription of the encoding region which the cells are undifferentiated.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

June 7, 2004